The Health and Environmental Sciences Institute (HESI) brings scientists from academia, government, industry, and NGOs around the world together to ensure the health and safety of people and our environment.

MOVING SCIENCE FORWARD

Science is advancing at a rapid pace, and building confidence and consensus around the latest advancements can be challenging. But these advancements also present exciting opportunities to use new data, research findings, and scientific breakthroughs to better protect human and environmental health. HESI has found that, by working collaboratively, the scientific community can better leverage new opportunities to enhance the efficiency and accuracy with which we address safety challenges facing humans and the environment.

As an independent non-profit, HESI is skilled at bringing together the right teams, asking the right research questions, and structuring the right frameworks and studies so that the newly available solutions inform decision-making by both private-and public-sector scientists. The research conducted by HESI teams is designed to move scientific principles into tested solutions that can be broadly applied to benefit health and the environment. HESI helps solve a broad range of public health issues including ways to improve drug safety for patients, protect the environment, and enhance the safety of the consumer products and foods we use every day.

HESI®

VISION

WE CREATE SCIENCE-BASED SOLUTIONS FOR A SUSTAINABLE, HEALTHIER WORLD.

PROVIDE sound science for better, more informed decisions.

BE the recognized leader in bringing together multidisciplinary teams to solve scientific challenges around risk assessment and safety.

ENCOURAGE collaboration across academia, government, industry, and NGO scientists.

CREATE AND TEST technology platforms and scientific frameworks that can be used to more effectively predict the effects on humans or the environment.

MISSION

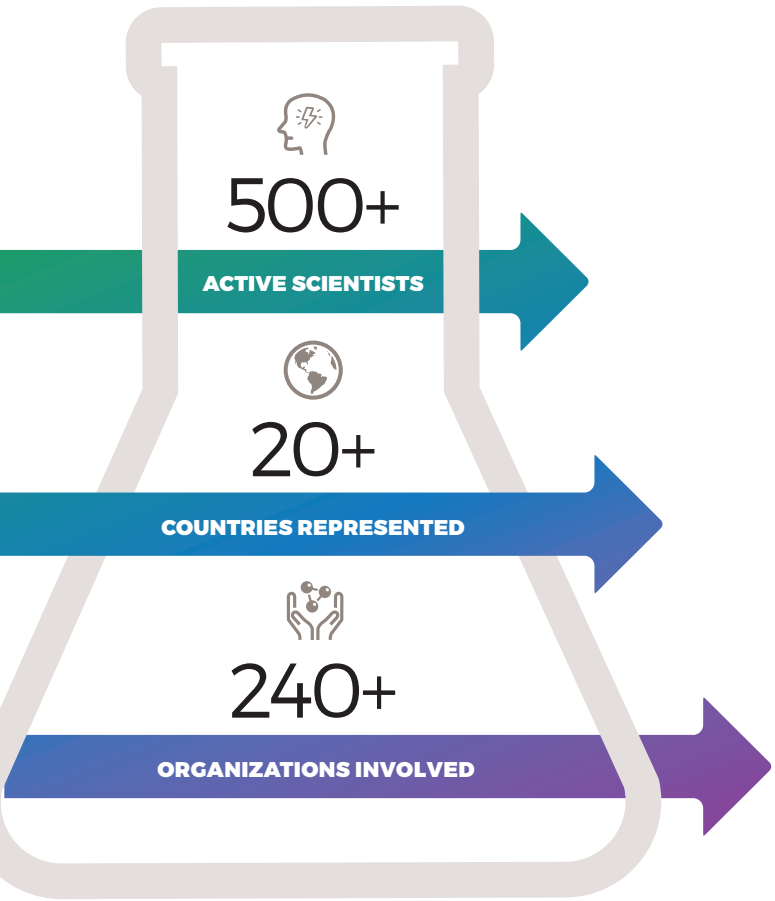
WE IDENTIFY AND RESOLVE GLOBAL HEALTH AND ENVIRONMENTAL CHALLENGES.

CREATE a collaborative environment where scientists from academia, government, industry, and NGOs come together to find solutions that improve health and environmental safety.

ENCOURAGE the development of meaningful studies that ask the right questions, structure the right framework, and develop solutions that inform decision-making by both private- and public-sector scientists.

CREATE a knowledge base that can be easily transferred from the laboratory or journal page to real life.

BY THE NUMBERS



VALUES

WE CREATE OPPORTUNITIES TO COLLABORATE.

We strive to make solving complex scientific problems more efficient by providing our members with access to the best minds around the world and encouraging them to come together to find solutions. By bringing together people from different backgrounds we promote innovative ways of looking at problems and improve the final outcome.

WE ARE DRIVEN BY SOLUTIONS.

Science that can be translated to solve every day problems is seen as more valuable and understandable. The research conducted by HESI technical committees is designed to use scientific principles to find and test real solutions that can be applied across fields of science.

WE ARE TRANSPARENT.

The data and findings that HESI's working groups produce are publicly available through the peer-reviewed literature, databases, and other means so that others can use it to guide their own research and enhance efficiency, often shortening project timelines and reducing budgets.

WE ARE INDEPENDENT.

We are an independent organization that advocates the use of science in making decisions that affect human and environmental health across the public and private sectors.

WE ARE COMMITTED TO EXCELLENCE.

Our technical committees are responsible for the hard, understated work of testing processes and frameworks that allow scientific data to be translated into solutions that protect the environment and human health.

HESI

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Developmental and Reproductive Toxicology (DART)

OUR MISSION

The DART Technical Committee provides a forum where scientists from industry, government, academia, and other key stakeholders can exchange information and initiate activities to advance science related to developmental and reproductive toxicology, and to develop consensus in the scientific community on the appropriate use of experimental toxicity data for human health risk assessment.

CHAIRS

Public Chair

Ms. Susan Makris (US Environmental Protection Agency)

Private Chair

Dr. Kary Thompson (Bristol-Myers Squibb Company)

HESI STAFF

Dr. Connie Chen
(cchen@hesiglobal.org)
Dr. Shermaine Mitchell-Ryan
(smitchell-ryan@hesiglobal.org)

2019 COMMITTEE HIGHLIGHTS

Participating Organizations

15 government/regulatory agencies, **9** academic/research institutes, **4** consulting, **22** industry

Publications

5 accepted/published, **1** submitted

Scientific Meetings and Trainings

- **4** committee meetings (2 commitee meetings; 2019 Teratology Society Meeting, Thyroid Hormone Assessment Symposium, San Diego, California; and European Teratology Society Annual Meeting, Cologne, Germany)
- **1** workshop (Thyroid Hormone Assessment Workshop, Washington, DC)

Web Tools and Assays

1 web tool

Outreach

- **1** poster (a poster on neonatal kidney physiology was presented at the Benelux Kidney Meeting in Eindhoven, The Netherlands)
- **1** presentation

Collaborations

1 within HESI, **1** external

- The Immunomodulation and Pregnancy Risk Work Group is a collaboration with the HESI Immuno-Safety Technical Committee that seeks to convene key stakeholders to discuss both current and novel methodologies in preclinical and translational safety assessment of pregnancy risk associated with immunomodulatory therapy.
- The HESI-ETS Thyroid Hormone Assessment Workshop was a joint effort with the European Teratology Society to collect information pertaining to analytical methodology and data on thyroid hormone levels in rodents.

Geographic Representation

Belgium, France, Germany, Japan, Netherlands, Sweden, Switzerland, United Kingdom, United States

WORKING GROUPS

- **Developmental Immunotoxicology.** This working group aims to gather disparate information on developmental immunotoxicology as it relates to testing in preclinical species into one authoritative manuscript.
- **Anogenital Distance and Nipple Retention.** To promote harmonization of anogenital distance (AGD) and nipple/areola retention measurement in male rats, this project aims to publish a review of existing methods and recommend best practices and considerations for these two methods.
- **Neonatal Pediatrics—Survey and Framework.** This working group aims to review and evaluate the available nonclinical literature for six key neonatal therapeutics areas (brain, lung and gastrointestinal injury, neonatal abstinence, infection, and retinopathy of prematurity) to help identify any common elements among the neonatal disease models or specific elements for each disease state.
- **Neonatal Pediatrics—Physiology.** This group aims to elucidate the comparative neonatal physiology/development of the ontogeny of absorption, distribution, metabolism and excretion (ADME)–related processes for multiple organ systems as it relates to preclinical animal models and the human neonate.
- **Neonatal Pediatrics—Starting Dose.** A white paper is being developed using case studies to demonstrate key considerations for nonclinical studies that would better inform starting therapeutic doses for neonatal populations.
- **Thyroid Hormone Assessments.** In collaboration with the European Teratology Society, the joint working group has collected historical data on thyroid hormone measurement in rodent studies to determine best practices for these measurements.

NEW **Pubertal Assessment.** This working group aims to identify reliable *in vivo* rodent markers and *in vitro* assays that are predictive of agents (chemical or pharmaceutical) that affect human puberty timing (and by puberty timing, this includes initiation, progression, and completion).

NEW **Juvenile Clinical Pathology Endpoints.** Clinical pathology data from control animals in previously conducted juvenile animal toxicity studies will be gathered. The goal is to author a manuscript that could be used as a reference across the industry.

NEW **Preclinical Considerations for Pregnant and Lactating Women in Clinical Tria**ls. A points-to-consider manuscript outlining initial approaches to inclusion, the role of nonclinical data, and common practices during global drug development plans is in development.

NEW **DARTable Genome.** This working group aims to enable better predictive toxicology by curating our knowledge of DART Molecular Initiating Events (MIE) and the quantitative Adverse Outcome pathways they trigger, to build a DART Safety Screening Panel.

NEW **microCT.** This work group aims to provide additional information and confidence that fetal skeletal examination using microCT is acceptable for regulatory use in nonclinical fetal evaluation studies.

- **Immunomodulators and Pregnancy Risk.** Key stakeholders will be convened to discuss both current and novel methodologies in preclinical and translational safety assessment of pregnancy risk associated with immunomodulatory therapy. The workshop will serve as starting point to address gaps in biology, current tools and other aspects of pregnancy risk that should be considered drug development.

NEW **QSAR Modeling of Rodent Placental Transfer.** This work group aims to improve developmental toxicological predictions by integrating exposure information into a preliminary QSAR model to predict placental drug transfer in rodents.

AREAS OF FOCUS FOR 2020

- The incorporation of computational chemistry/biology and modeling projects to place the committee at the frontier of emerging innovation and tools in the DART field
- Validation of alternative methods, new concepts or new systems of models for assay validation, and creating a validation framework for non-animal methods

STRATEGIC IMPACT AREAS

Enhanced Efficiency and Accuracy in Safety Assessment Practice

Various projects within the portfolio focus on the harmonization of current regulatory guidance related to developmental and reproductive toxicology, as well as recommending best practices for assessing the risk/safety associated with the exposure of teratogenic agents. This includes but is not limited reviewing test data and current methods for identifying disruptions in developmental/reproductive maturation or function in preclinical species resulting from exposure while evaluating the translational value across species and in humans.

Enhancement of the Societal Knowledge Base on Human Biological Processes of Relevance for Protecting Human Health

Many of the efforts that initiated under the HESI DART pediatrics project seek to further elucidate mechanisms within the critical windows in development and reproduction and to better understand the ontogeny of ADME processes that dictate the disposition of a putative teratogen with an organism.

PUBLICATIONS

Cassar S, Beekhuijzen M, Beyer B, Chapin R, Dorau M, Hoberman A, Krupp E, Leconte I, Stedman D, Stethem C, van den Oetelaar D (2019) A multi-institutional study benchmarking the zebrafish developmental assay for prediction of embryotoxic plasma concentrations from rat embryo–fetal development studies. *Reproductive Toxicology*. 86:33–44. doi: 10.1016/j.reprotox.2019.02.004.

De Schaepdrijver LM, Annaert PP, Chen CL (2019) Ontogeny of ADME processes during postnatal development in man and preclinical species: a comprehensive review. *Drug Metabolism and Disposition*. 47(3):295. doi: 10.1124/dmd.118.084350.

Hausner EA, Elmore SA, Yang X (2019) Overview of the components of cardiac metabolism. *Drug Metabolism and Disposition*. 47(6):673–688. doi: 10.1124/dmd.119.08661.

Neal-Kluever A, Fisher J, Grylack L, Kakiuchi-Kiyota S, Halpern W (2019) Physiology of the neonatal gastrointestinal system relevant to the disposition of orally administered medications. *Drug Metabolism and Disposition*. 47(3):296–313. doi: 10.1124/dmd.118.084418.

Skaggs H, Chellman GJ, Collinge M, Enright B, Fuller CL, Krayer J, Sivaraman L, Weinbauer GF (2019) Comparison of immune system development in nonclinical species and humans: closing information gaps for immunotoxicity testing and human translatability. *Reproductive Toxicology*. 89:178–188. doi: 10.1016/j.reprotox.2019.06.005.

Bueters et al. Ontogeny and cross species comparison of pathways involved in drug absorption, distribution, metabolism and excretion in neonates: kidney. *Drug Metabolism and Disposition. Submitted.*

PARTICIPATING ORGANIZATIONS

Government/ Regulatory Agencies

Federal Agency for Medicines and Health Medical Products Agency (Sweden)
Federal Institute for Medicines and Health Products (Belgium)
Health Canada
Medicines and Healthcare Products Regulatory Agency (UK)
Medicines Evaluation Board (The Netherlands)
Medicines for Malaria Venture
National Agency of Medicine and Health Products Safety (ANSM, France)
National Institute for Quality and Organizational Development in Healthcare and Medicines (Hungary)
National Institute of Environmental Health Sciences, National Toxicology Program
Paul Ehrlich Institute (Germany)
Pharmaceutical and Medical Devices Agency (Japan)
Swedish Chemical Agency
US Environmental Protection Agency
US Food and Drug Administration
US Office of Management and Budget

Academic/ Research Institutes

Creighton University School of Medicine
Erasmus University
Georgetown University
Ghent University
Howard University
Karolinska Institute
McMaster University
National Institute for Public Health and the Environment (RIVM, The Netherlands)
Radboud University, Nijmegen Medical Centre

Consulting

Aclario Pharmaceutical Developmental Group, Inc.
ApConiX, Ltd.
Critical Path Institute
Exponent

Industry

AbbVie
Amgen Inc.
AstraZeneca AB
Bayer
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Celgene Corporation
Charles River Laboratories
Corteva Agriscience
Covance
Eli Lilly and Company
ExxonMobil Biomedical Sciences Inc.
Genentech
GlaxoSmithKline
Janssen Pharmaceuticals
Merck & Co., Inc.
Pfizer Inc.
Procter & Gamble Company
Roche
Sanofi
Syngenta
Takeda Pharmaceutical Company Limited